

REMARKS

I. STATUS OF CLAIMS

Claims 1-37 are pending in this application. Claims 1-17, 19, 26, 28, 29, 31, and 33-37 are withdrawn from consideration as directed to non-elected subject matter. Claims 18, 21-25, 27, 30, and 32 are under examination and stand rejected. No amendments are made herein.

II. REJECTION UNDER 35 U.S.C. § 103(a)

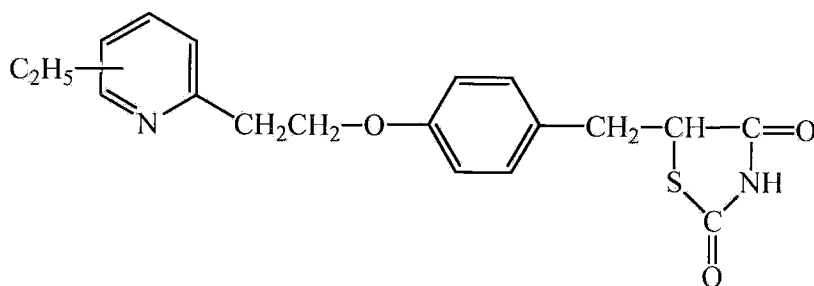
A. Sasaki and Patani

Claims 18, 21-22, 27, 30, and 32 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Sasaki et al. (J. Org. Chem., 1976, 41 (7), 1100-1104) ("Sasaki") in view of Patani et al. (Chem. Rev. 1996, 3147-3176) ("Patani") for the reasons of record. Office Action at page 3. Applicants continue to disagree with the rejection and respectfully submit that a *prima facie* case of obviousness has not been established for at least the following reasons.

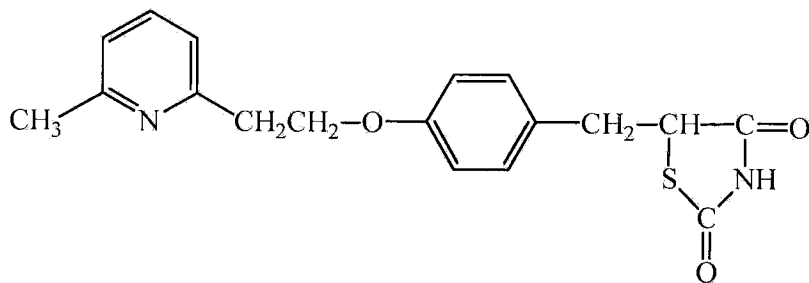
In a decision analyzing the standard for obviousness of chemical compounds, the Federal Circuit clearly indicated that the first step in this analysis is the identification of a "lead compound" that can be used as a starting point for modification to arrive to the claimed compounds. *Eisai Co., Ltd. v. Dr. Reddy's Laboratories*, 87 U.S.P.Q.2d at 1457, 533 F.3d at 1359. This explicit requirement followed the rationale in another post-*KSR* Federal Circuit case specifically addressing an obvious-to-try argument in the context of chemical compounds. *Takeda*, 83 U.S.P.Q.2d at 1176, 492 F.3d at 1359. Of particular note is this requirement applies even when following an "obvious-to-try" rationale, as the Examiner does here.

The *Takeda* court indicated that even under an obvious-to-try argument, it was still necessary to identify a lead compound. Once a suitable starting point has been established, there must also be "a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.'" *Takeda*, 83 U.S.P.Q.2d at 1174, 492 F.3d at 1356 (citations omitted). The Court explained that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new compound." *Id.* (underlining added).

In *Takeda*, the patented compounds had the general formula (claim 1):



The compound in the prior art, "compound b," was identical to the patented compounds, except that a methyl group, instead of an ethyl group, was attached to the pyridyl ring located on the left hand side of the molecule, as indicated in the drawing below. *Takeda*, 83 U.S.P.Q.2d at 1172, 492 F.3d at 1354.



Because the structure of the patented compounds allowed the substitution by the ethyl group on any available carbon atom in the pyridyl ring, the only difference between the prior art compound and the claimed compounds was a methylene group ($-\text{CH}_2-$) in the alkyl radical of the pyridyl ring. *Id.* From a comparison of the above structures, it is evident that the degree of similarity between the prior art compound and the patented compound is extremely high. Yet, the court in *Takeda* found the claims not obvious because there was no suggestion to prepare the claimed compounds in light of the prior art compound. *Takeda*, 83 U.S.P.Q.2d at 1176-77, 492 F.3d at 1360.

These decisions require at least that the Examiner: (1) identify a compound that would have been considered by one of ordinary skill in the art as suitable for further modification, and (2) explain the reasons why the skilled artisan would have then made the specific modifications proposed by the Examiner to arrive at the claimed invention.

Applicants submit that the Examiner has not met this burden for at least the following reasons.

1. The Examiner has not shown that compound 4 of Sasaki would have been considered a suitable lead compound for further modification

The Examiner contends that despite Sasaki's disclosure that compound 4 resulted in some uncertainty regarding its structural resonance, "compound 4 would be the end product and would reasonably be considered a lead, along with the related compound 3," and therefore,

there would be an expectation that [compound 4] would be among the compounds which show biological activity, or at least provide motivation to the skilled artisan to test the compounds for biological activity with an expectation of

success where some compounds which are structurally similar have been of biological interest.

Office Action at page 4. Applicants disagree.

The Examiner has not provided any reasonable motivation to choose compound 4 for modification that would lead to Applicants' claims. For example, the Examiner's conclusion that "compound 4 would be the end product," is incorrect and not supported by Sasaki. Sasaki explicitly states that "[c]ompound 4 could be reconverted to 3a." Sasaki at page 1101; see *a/so* figure on page 1100, demonstrating conversion of compounds 4 and 3a. Indeed, from this teaching, and from Sasaki as a whole, one of ordinary skill in the art would understand that compound 4 is neither an "end product," nor a lead compound.

Moreover, Sasaki teaches at least 4 mechanisms for synthesizing compound 3a, only one of which yields compound 4. The first mechanism is the reaction of compound 2a with sodium azide in DMF, which resulted in only compound 3a. Sasaki at page 1100. Compound 3a was also synthesized "in a similar but shorter time reaction," from compound 2b. Sasaki at pages 1100-1101. The third mechanism, i.e., the reaction of compound 2c with sodium azide in DMF, which was investigated because the previous two "rendered the analysis rather cumbersome," did result in compound 4, in addition to "another possible structure, iii" Sasaki at page 1101. Because the third synthetic mechanism was ambiguous, Sasaki teaches that a fourth "unambiguous synthesis of 3a was attempted," which Applicants note does not result in compound 4. Sasaki then goes on to discuss some additional reaction mechanisms utilizing compound 3a as a starting reactant, e.g., conversion of compound 3a into compound 9 and compound 9'

and reaction mechanisms involving compounds 10-15 (none of which form compound 4). Sasaki at pages 1101-1102. Thus, the only disclosure of compound 4 is in an ambiguous synthetic mechanism utilized to prepare compound 3a. Clearly, Sasaki's goal was to synthesize compound 3a. While the Examiner states that compound 4 "would reasonably be considered a lead," there is no basis, absent impermissible hindsight, for this conclusion. The Examiner points to no basis on which one of ordinary skill in the art would choose compound 4 from all fifteen compounds taught in Sasaki. In fact, the evidence in Sasaki clearly weighs against a finding that one of ordinary skill in the art would have selected compound 4 for further modification out of all of the compounds disclosed in Sasaki.

For this reason, the Examiner has failed to meet the standards set out in *Eisai* and *Takeda* as well as the requirements for an "obvious to try" rationale. Even Patani, the reference cited by the Examiner, indicates Patani's teachings should be applied to lead compounds. Specifically, Patani only suggests "modification of lead compounds." Patani at page 3147, col. 2 (emphasis added). That is, the teachings of Patani are applicable once one of ordinary skill in the art has identified a suitable compound as a lead compound for modification in order to obtain "safer and more clinically effective agents." *Id.* The Examiner has not explained why one of ordinary skill in the art considering the teachings in Patani would have considered compound 4 a "lead compound," so that the teachings in Patani could be applied to its modification. Instead, the Examiner impermissibly relies on hindsight to choose a compound from Sasaki that might be modified. See M.P.E.P. § 2142 ("impermissible hindsight must be avoided and

the legal conclusion [of obviousness] must be reached on the basis of the facts gleaned from the prior art”).

The Examiner asserts “[w]hile Patani et al does discuss modifying a lead compound, it does not define the term ‘lead compound’ in the limiting manner that Applicants assert.” Office Action at 4. Applicants respectfully submit that the meaning for a “lead compound” as indicated in the previous Response, and herein, is understood in the same manner as in *Takeda*. That is, one of ordinary skill in the art, in order to “identify predictable solutions,” would first identify a lead compound suitable “for further investigation,” i.e., modification. The Examiner has pointed to nothing suggesting an alternative definition. Under the guidance of *Takeda*, one of ordinary skill in the art would not have been motivated to select compound 4 for modification. This is because compound 4 results from only one *ambiguous* synthetic mechanism for the formation of another compound, compound 3a, and produces “irregular resonances” resulting in “uncertainty” in the interpretation of its NMR spectrum. Thus, one of ordinary skill in the art would have been discouraged from selecting compound 4 for modification because of its inherent uncertainties, and consequently, would have been motivated if at all to select another compound of Sasaki resulting in less ambiguous and less uncertain results.

For at least this reason, Applicants respectfully request that this rejection be reversed.

2. The references cited by the Examiner fail to suggest the modifications advanced by the Examiner to arrive at the claimed compounds

As discussed in *Takeda*, “a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention” is also a necessary requirement in obviousness rejections of chemical compounds.

Takeda, 83 U.S.P.Q.2d at 1174, 492 F.3d at 1356 (citations omitted).

In the instant rejection, the Examiner states that

while Patani et al discloses a number of bioisosterism modifications, they are not numberless and the skilled artisan would simply pick and choose from among the disclosed potential substitutions to result in the instant compounds. Note, the bioisosteres would all be reasonably expected to have similar functional properties as the compound to be modified, given the teaching is to optimize the effective agent into a more effective agent.

Office Action at page 5. Applicants respectfully disagree.

The Examiner’s rationale ignores Patani's results showing that substitutions can result in unpredictable effects, e.g., can result in lower biological activity of the resulting compound. For example, Patani teaches that the “[r]eplacement of the sulfur atom at C-8 [of compound 30] with the oxygen or selenium atom . . . resulted in weaker activity relative to the thio analogue.” Patani at page 3155, see *also* Table 18.

To the extent that a conclusion can be drawn from reviewing the data in Patani critically, one of ordinary skill in the art would surmise that not all bioisosteric substitutions result in similar biological activity as indicated by the Examiner. As discussed in the previous Response, Patani provides only a qualitative review of

designing drugs using bioisosteric replacement, and does not in any way make predictions regarding the effects of modifying a specific compound.

Applicants note that *Takeda* was decided after the landmark case of *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). The Federal Circuit in *Takeda* specifically addressed the arguments on which the Examiner seems to base this rejection, namely, structural similarity (compound 4 from Sasaki differing at least in the presence of a carbonyl instead of an imine group from the claimed compounds) and the ability of one of ordinary skill in the art to make the modification (Patani allegedly teaching bioisosteres of the carbonyl group). The *Takeda* court commented that “[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of ‘adequate support in the prior art’ for the change in structure.”

Takeda, 83 USPQ2d at 1174, 482 F.3d at 1356. The Federal Circuit further explained:

We elaborated on this requirement [to show adequate support in the prior art for the change in structure] in the case of *In re Deuel*, 51 F.3d 1552, 1558 [34 USPQ2d 1210] (Fed. Cir. 1995), where we stated that “[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound.” That is so because close or established “[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds.” *Id.* . . . We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the “prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention” was also required. *Id.*

Id. (emphasis added, internal citations omitted). That is, more than the mere ability to make the modification is required to prove obviousness - the Examiner needs to show that the “prior art would have suggested making the specific molecular modifications

necessary to achieve the claimed invention.” Therefore, the Examiner’s argument that “the skilled artisan would simply pick and choose from among the disclosed potential substitutions to result in the instant compounds” is inadequate to support this rejection.

For at least this additional reason, the Examiner has not made a *prima facie* case of obviousness and Applicants respectfully request that this rejection be reversed.\

B. Sasaki, Patani and Gilbert

Claims 23-24 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sasaki and Patani, and further in view of Gilbert et al. (Antimicrobial Agents and Chemotherapy, 1986, Vol. 30, No. 2, pp. 201-205) (“Gilbert”) for the reasons of record. Office Action at page 5. Applicants respectfully disagree and traverse the rejection for at least the following reasons.

Gilbert is solely relied upon for its teaching of “the inclusion of an antiviral.” Office Action, dated November 23, 2009, at page 5. Indeed, Gilbert is focused on the characterization of ribavirin, such as its “chemical structure, possible mode(s) of action, metabolic disposition, and clinical use as an antiviral agent.” Gilbert at Introduction. Claims 23 and 24 depend from claim 21, and therefore incorporate all the limitations of claim 21. And as discussed above, Sasaki and Patani do not render, *e.g.* claim 21 obvious because one of ordinary skill in the art would not have selected compound 4 of Sasaki as a lead compound and would have had no motivation to further modify compound 4 to make the compounds encompassed by claim 21. Applicants respectfully submit that Gilbert does not remedy the deficiencies of Sasaki and Patani, and therefore the rejection is improper and should be withdrawn.

III. CONCLUSION

In view of the foregoing remarks, Applicants respectfully request reconsideration this application and the timely allowance of the pending claims.

If the Examiner believes a telephone conversation might advance prosecution, the Examiner is invited to call Applicant's undersigned representative at 202-408-4265.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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GARRETT & DUNNER, L.L.P.

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